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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,724	09/22/2000	Pramod K. Srivastava	8449-128-999	1804

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,724	SRIVASTAVA, PRAMOD K.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,71 and 76-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,71 and 76-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Srivastava *et al*
Priority Date: 02 June 2000

1. The amendment filed 11/08/2004 is acknowledged and entered into the record. Accordingly, claims 1-30,32-70,72-75, and 83, are canceled without prejudice or disclaimer.

2. Claims 31,71, and 76-93 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The Information Disclosure Statement filed 11/8/04 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112, 1st paragraph

5. The rejection of claims 31,71,76, 80-91 under 35 USC § 112, 1st paragraph as lacking written description is maintained for the reasons of record. Applicant's arguments are based on establishing and arguing for adequate written description for the newly amended claims limitations of α2 macroglobulin (α2M) fragments, α 2M receptor fragments, and heat shock protein (HSP) fragments.

More specifically applicant contends that the specification provides written support for:

a) α2M fragments (i.e. at least 5 consecutive amino acids of the α2M) because their functional (ability to bind to α2M receptor) and structural (boundaries of the α2M receptor binding domain) descriptions have been disclosed and concludes that a correlation between structure and function is described;

b) HSP fragments (those that bind to the α2MR) whose structure have been defined by reference to exemplary HSPs; and

c) α2MR fragments (i.e. at least 5 consecutive amino acids of the α2MR) because a fragment of the α2MR (i.e. the extracellular domain, figure 8b) and functional aspects (i.e. binding to HSPs) have been disclosed.

Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. This case is analogous to Example 13 of the written description guidelines. Specifically, the examples indicates that when a genus is represented by a single species, the specification and the claims must provide distinguishing attributes that are shared by the members of the genus. In the instant case, the structure of α2M is well established in the art, however, neither the specification or the claims provide sufficient description of which portions of α2M are encompassed as fragments. With regard to the HSP fragments, general reference to HSPs is not adequate disclosure of the intended fragments, because no defining structure coupled to a functional activity is provided for

the genus of fragments claimed. The reliance of portions that bind to α2MR is a general description of HSPs, no sequence of this portion has been disclosed. In regard to α2MR, the disclosure of a single species does not adequately represent the full breadth of α2MR fragments encompassed. Again, no structure function relationship has been made in the specification or the claims. No structural detail other than the minimum number of amino acids (i.e. for α2M) in the fragment is disclosed in the specification, no partial structure or core motifs are provided in the specification, and no functional activity that correlates structure and function are provided in the specification or in the claims. Applicant's reliance on general structure (i.e. α2MR binding domain) and function (i.e. ability to bind α2MR) is inadequate because specific not general disclosure is required, so that one of skill in the art can distinguish the product used from others in the same class and also to show in such full, clear, concise, and exact terms that the skilled artisan would recognize that the applicant was in possession of the genus claimed.

6. Therefore, the rejection of the claims under 35 USC 112, 1st paragraph as lacking adequate written description is maintained for the reasons of record.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The rejection of claims 31,71,and 76-93 as lacking an enabling disclosure under 35 USC § 112, 1st paragraph is maintained for the reasons of record. Applicant argues that the disclosure of the instant application enables methods of inhibiting or modulating an immune response because the utility is supported by cell-based assays. More

specifically, applicant contends that in an in vitro cell-based assay, antibodies against α2MR inhibited the re-presentation of HSP-peptide complexes. Applicant asserts that this inhibition in vitro is indicative of in vivo success because the assay uses cells involved in immune responses in vivo. From this, applicant concludes that it would not be unreasonable to extrapolate in vitro cell culture assays to cells in vivo because the mechanism of peptide presentation is maintained. To support these conclusions, applicant relies on Binder *et al* (2004--IDS no. C02) who teach the in vivo effects of α2M and α2MR antibodies on the representation of the gp96-ova peptide complex; Binder *et al* (2002 – IDS no. C03) who teach similarly that the administration of anti-α2MR antibodies inhibited the growth of Meth A fibrosacrcomas; and Basu *et al* (2001 – IDS C04) who showed that anti-α2MR antibodies were able to interfere with the interaction of HSP with the α2MR. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. Applicant supports enablement of the instant invention by indicating that cells used in the in vitro assays are the same as those in vivo. However, as indicated in the last office action, cells in vitro behave differently from those in vivo (see Freshney *et al*). The cells (i.e. macrophage cells – as indicated in the response on page 11) used in the working examples of the instant application (i.e. example 6, page 72) are RAW264.7 macrophage cell lines (see page 71). Thus as indicated by Freshney *et al*, it would be

unpredictable to those of skill in the art at the time the invention was made or filed, that the success of inhibiting re-presentation in a macrophage cell lines would be indicative of its ability to do so in vivo because the characteristics or behaviors of the in vitro cell are different from those that actually exist in vivo. Applicant's reliance on post filing evidence to show that antibodies to α2MR are effective in modulating immune responses, in treating cancer, and in interfering with HSP interactions with α2MR does not supplement the knowledge at the time of filing. One of skill in the art practicing the invention as outlined in specification would not have a reasonable expectation of success in practicing the invention because of the unpredictability in the art with regard to using in vitro cell lines as indicators of in vivo success.

Applicant additionally argues that the specification teaches that in vitro assays using α2MR fragments, HSP fragments and α2M fragments were able to interfere with or modulate α2MR related immune responses (see page 13 or response). Applicant also asserts that post filing date references enable the use of α2MR, HSP, and α2M fragments for the in vivo modulation of an immune response. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Again, as outlined above, it would not be predictive based on the teachings of Freshney *et al*, for example that the results obtained in vitro would be indicative of in vivo modulation or inhibition. The fact that references made available post-filing demonstrated in vivo modulation or inhibition does not supplant the lack of knowledge at the time of filing.

Finally, applicant also contends that claims 31 and 71 are drawn to modulation of immune responses and or inhibiting immune responses, and that issues regarding treatment of cancer are irrelevant to the instant claims. Applicant also argues that in vitro data is sufficient so long as it correlates with in vivo response to cancer. Applicant again relies on Binder *et al* (2004 and 2002) to support that a correlation can be made between in vitro and in vivo tumor response. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The claims are drawn to a method of modulating an immune response and inhibiting an immune response which encompasses treatment of cancer and therefore falls within the scope of the claims. With regard to correlation of in vitro and in vivo response, the cell lines used in the instant applicant cannot be adequately correlated to its counterpart in vivo because of the behavioral and functional differences associated with in vitro cell lines.

Thus the rejection of claims under 35 USC 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record.

New Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 76 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

10. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. In the present instance, claim 76 and 84 recites the broad recitation antagonist and peptide, respectively, which is broader than the limitation of the narrower set of compounds recited in claim 31 and 71. In other words, an antibody, α2MR fragment, HSP fragment, and α2M fragment are species of the genus antagonist and peptide later recited.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 11/08/2004.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
February 1, 2005

GARY NICKOL
PRIMARY EXAMINER